

## Phenotypic association analyses with copy number variation in recurrent depressive disorder

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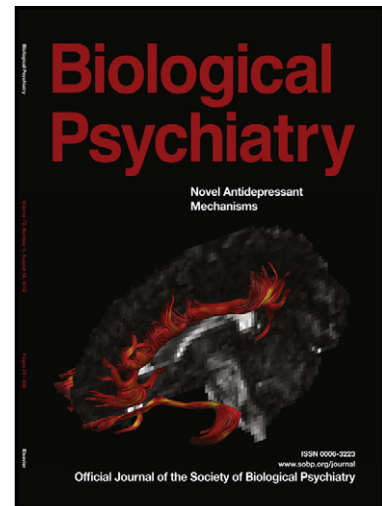
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# Phenotypic Association Analyses With Copy Number Variation In Recurrent Depressive Disorder

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## Abstract

**BACKGROUND:** Defining the molecular genomic basis of liability to depressive disorder remains a considerable challenge. We have previously associated rare, exonic deletion copy number variants (CNV) with recurrent depressive disorder (RDD). Sex chromosome abnormalities have also been observed to co-occur with RDD.

**METHODS:** In this re-analysis of our RDD dataset (n=3,106 cases, 459 screened controls and 2,699 population controls) we further investigate the role of larger CNVs and chromosomal abnormalities in RDD, and perform association analyses with clinical data derived from this dataset.

**RESULTS:** We find an enrichment of Turner's syndrome among cases of depression when compared to the frequency observed in a large population sample (n=34,910) of live-born infants collected in Denmark (2 sided  $p=0.023$ , OR 7.76 (95% CI 1.79 - 33.6)), a case of diploid/triploid mosaicism and several cases of uniparental isodisomy. In contrast to our previous analysis large deletion CNVs were no more frequent in cases than controls, although deletion CNVs in cases contained more genes than controls (2 sided  $p=0.0002$ ).

**CONCLUSIONS:** After statistical correction for multiple comparisons our data does not support a substantial role for CNVs in RDD, although (as has been observed in similar samples) occasional cases may harbour large variants with aetiological significance. Genetic pleiotropy and sample heterogeneity suggest that very large sample sizes are required to conclusively study the role of genetic variation in mood disorders.

## Introduction

Recurrent major depressive disorder (RDD) is associated with high morbidity, high economic burden and high rates of suicide(1-4). The genomic basis of liability to RDD is largely unknown(5). Twin studies have suggested that recurrent and severe forms of major depressive disorder are particularly heritable forms(6; 7), however genome

wide association studies (GWAS) with single nucleotide polymorphisms (SNPs) have shown inconsistent results(8; 9) and a recent mega-analysis failed to find any genome-wide significant associations(10), suggesting that other forms of genetic variation may be responsible for the observed heritability. Large, rare copy number variants (CNVs), defined as deletions or duplications of genomic material > 1,000 base pairs in length, have been identified and associated with a range of psychiatric disorders(11-15), although the evidence for association with mood disorders is not yet clear(16-20). We have previously shown an enrichment of rare, exonic deletion CNVs in a sample of RDD, with a low frequency of such variants in a screened control sample(20). Large chromosomal abnormalities are also easily detectable by DNA microarray(21). A variety of such abnormalities, particularly sex chromosome aneuploidies(22; 23) and the 22q11.2 microdeletion(24), have been associated with psychiatric diagnoses such as schizophrenia and mood disorders, although association with any specific phenotype is usually incomplete(25).

We investigated the frequency of sex chromosome aneuploidies and large, rare CNVs in 3,106 cases of RDD. We hypothesized that chromosomal aneuploidies; large (>100kb), rare CNVs; and particularly CNVs located in regions previously associated with psychiatric disorders, may be associated with a diagnosis of RDD, a younger age of onset, longer duration of illness and measures of neuroticism, psychoticism and extraversion made in our dataset. We compared our case sample to a control sample screened for a lifetime absence of psychiatric disorder (n=459), and an unscreened population control sample (n=2,699) from phase 2 of the Wellcome Trust Case Control Consortium (WT2) and, for sex chromosome aneuploidies only, to data from karyotype analysis undertaken in 34,910 sequentially screened live-born infants in Denmark reported by Nielsen and Wohler(26).

## **Materials & Methods**

### **Samples**

3,106 cases (2,197 female & 909 male) were taken from three studies of RDD; the Genome Based Therapeutic Drugs for Depression (GENDEP)(27); the Depression

Network study (DeNT)(28) and the Depression Case Control study (DeCC)(29). This sample set is almost identical to that analysed in(20), however calling methods and quality control procedures have been updated and varied according to the length of CNV being called. Further details of the contributing studies are provided in the supplementary information. All samples were derived from venous blood collected at the time of interview and extracted in the same laboratory. All samples are from individuals with European origin. Informed written consent was obtained from all participants. All studies were approved by relevant local ethics committees.

As an additional control set we used 2,699 control samples (1,354 female & 1,345 male) run on Illumina Infinium 1M bead arrays from phase 2 of the Wellcome Trust Case Control Consortium (WT2) representing the national blood service cohort, derived from subjects who have donated blood to the UK blood services collection.

### **Phenotypic Data Collection and Extraction**

The phenotypic data from across studies included in this dataset has been previously curated into a single database(30). We extracted data on the following items.

1. Age of first onset of disorder
2. Duration of worst episode
3. Trait neuroticism scores
4. Trait psychoticism scores
5. Trait extraversion scores

Trait personality scores are derived from the Eysenck Personality Questionnaire(31) (see supplementary information for more detail).

### **Genotyping**

Samples were genotyped on the Illumina (San Diego, CA, USA) HumanHap 610-Quad Beadchip, contemporaneously processed at the same laboratory. Raw probe intensity data was processed according to the manufacturer's guidelines with Illumina's GenomeStudio platform to obtain the normalised probe intensity at each marker and the log R ratio (LRR) and B allele frequency (BAF) at each marker.



## **CNV Calling**

To make CNV calls we processed fluorescence intensity data for autosomal markers common to each Illumina array (n=562,680) using three separate algorithms; PennCNV(32) (version released August 2009); QuantiSNP v2.3(33) and iPattern(34) in liaison with the authors.

## **Sample and CNV Quality Control**

We analysed all samples for chromosomal aneuploidies, since they are rare and pragmatic to visually confirm. We used measures of the heterozygosity of the BAF calculated by PennCNV for chromosome X and the mean of the Log R Ratio of chromosome Y, calculated in R(35), to make two predictions of gender for each sample, and then looked for discordances between the two predictions. As well as comparing the frequency of sex chromosome aneuploidy in our case and control sets, we also compared with the frequency detected in 34,910 sequentially screened live-born infants from an observational study by Nielsen and Wohler(26).

To detect autosomal aneuploidy we calculated the LRR mean and BAF heterozygosity for each chromosome and visually inspected plots where this value deviated by more than 3 standard deviations from the mean for the value taken across all autosomes in that sample.

For phenotypic association analyses we used sample-wide quality control (QC) metrics calculated by Genome Studio and the PennCNV algorithm as well as additional metrics calculated with code derived from the CNVision package (<http://futo.cs.yale.edu/mw/index.php/CNVision>). For detailed methods, including specific thresholds and CNV merging definitions, see supplementary information.

## **CNV Validation**

To validate a subset of our CNV calls we used a customized high density oligonucleotide comparative genomic hybridization (CGH) array from Agilent(4x180k, Agilent Technologies, CA, USA) in liaison with Oxford Genome Technologies (Oxford, UK). 183 samples from our cases and screened controls were

analysed on the CGH array. Of 183 samples, 36 CNVs in 35 samples were available for follow up. All 36 CNVs (100%) were validated. Full details of the regions used for follow up, CNVs available for validation and further information regarding array CGH laboratory protocols, can be found in the supplementary information.

### **Power Calculations**

Power calculations in CNV studies are problematic as effect sizes and models of association are based on approximations that may not be realistic. For comparisons of sex chromosome abnormalities, a post hoc calculation of power given our figures for Turner's syndrome suggests we have a 99% power to detect a significant effect. For analyses of large CNVs, assuming a three-fold enrichment between cases and controls we have 75% power to detect an effect. For phenotypic analyses, on the assumption of a linear model of association with phenotype, a rare variant effect size of 0.005 and a type 1 error probability of 0.05, we calculate that our sample size has 88% power to detect an effect from rare CNVs occurring over the whole genome.

### **Statistical Analysis**

Frequencies of samples with large CNVs and aneuploidies were compared with Fisher's exact test (p values for 1 and 2 sided tests shown). Whole genome analyses of CNV burden between cohorts were performed using permutation analysis in PLINK v1.07. An initial  $\alpha$  level of 0.05 was set. Burden analyses were divided into three sets of tests- cases vs. all controls, cases vs. screened controls and cases vs. WT2 controls. Each of these sets of larger analyses was further subdivided into analyses considering all CNVs, deletion CNVs and duplication CNVs. Within these subsets of analysis 7 individual burden tests were performed, resulting in a total of 63 burden tests (see supplementary information for more detail). We therefore set a Bonferroni corrected significance p value of 0.00079. This significance level is likely to be conservative as the datasets are not independent. For phenotypic analysis we set an initial  $\alpha$  level of 0.05, then used matrix spectral decomposition of the correlation matrix between the 5 phenotypic variables analysed(36), implemented at <http://gump.qimr.edu.au/general/daleN/matSpD/>, resulting in a corrected  $\alpha$  level of 0.0073. Statistical association with phenotypic data was performed using linear

regression implemented in STATA IC v10.1(37). Power calculations were performed with G\*Power v3.1.7 and the 'pwr' package (version 1.1.1), implemented in R(35).

## Results

### Sex Chromosome and Autosome Aneuploidies

All 3,106 case samples were analysed for sex chromosome aneuploidy. Of 2,197 female cases we detected 3 cases of 45,X (Turner's syndrome) (Fig. S2A) of which 2 were probable 45,X/46,XX mosaics (Fig. S2B). Of 909 male cases we detected two cases of 47,XXY (Klinefelter's syndrome), one of which had an additional deletion of Yq (Fig. s3). Significantly more cases of 45,X were observed in our case sample when compared to the population sample (n=34,910) of live-born infants reported by Nielsen and Wohler(26) (2 sided p=0.023, OR 7.76 (95% CI 1.79 - 33.6)). No other comparisons were statistically significant. 1 case of 47,XXY (Klinefelter's syndrome) was detected in the WT2 controls. Full results are presented in table 1.

<<Table 1 about here>>

We detected no autosomal aneuploidies. We detected one case of diploid/triploid mosaicism (Fig. s4). Three cases were found to harbor complete uniparental isodisomy (UPD) for a single chromosome (1 in chromosome 12 (Fig. S5A) and 2 in chromosome 4 (Fig. S5B & Fig. S5C)). Two samples from the WT2 control group were also found to harbor UPD of a whole chromosome (1 of chromosome 13 (Fig. S5D) and 1 of chromosome 21 (Fig. S5E) (1 sided p=0.57, 2 sided p=1.00, OR=1.30 (95% CI 0.26 -  $\infty$ )). No samples from the screened control group showed UPD (1 sided p=0.66, 2 sided p=1.00).

### Large CNVs

Large CNVs are defined as having length >1MB and called with >100 markers. All CNV details are published in supplementary table s3. Large CNV frequencies are shown in table 2.

<<Table 2 about here>>

5,430 samples passed sample QC (2,723 case samples, 348 screened control samples and 2,359 WT2 control samples). 126 CNVs larger than 1MB were detected in 123 (2.3%) samples. Of these CNVs, 36 (28.5%) were heterozygous deletions and 90 (71.5%) were heterozygous duplications. 3 CNVs (2.4%) were greater than 5MB in size, 2 (1.6%) between 3 and 5MB in size, 11 (8.7%) between 2 and 3MB in size, and the rest (110 (87.3%)) between 1MB and 2MB in size.

Of 2,723 case samples we detected 77 CNVs in 74 samples. Of 348 screened control samples we detected 4 CNVs in 4 samples (2 sided  $p=0.10$ ,  $OR=2.40$  (95% CI 0.91 - 6.36)). Stratifying by CNV type, 21 deletion CNVs were observed in 20 cases, whilst 2 deletion CNVs were observed in 2 controls (2 sided  $p=1.00$ ,  $OR=1.28$  (95% CI 0.33 - NaN)). 56 duplication CNVs were observed in 54 cases, whilst 2 duplication CNVs were observed in 2 controls (2 sided  $p=0.084$ ,  $OR=3.46$  (95% CI 0.93 - NaN)).

Of 2,359 WT2 control samples we detected 45 CNVs in 45 samples. As stated above, 77 CNVs were seen in 74 case samples (2 sided  $p=0.063$ ,  $OR=1.44$  (95% CI 0.99 - 2.09)). Stratifying by CNV type, again 21 deletion CNVs from 20 cases were observed in our case sample, whilst in the WT2 control sample 13 deletion CNVs were observed in 13 samples (2 sided  $p=0.49$   $OR=1.34$  (95% CI 0.67 - 2.65)). 56 duplication CNVs were observed in 54 cases, whilst 32 duplication CNVs were observed in 32 WT2 controls (2 sided  $p=0.10$ ,  $OR=1.45$  (95% CI 0.94 - 2.25)).

141 cases (37 males and 104 females) demonstrated mood-congruent psychotic symptoms. Within this subset there were 5 CNVs in 5 cases (2 male and 3 female). We compared this to CNV frequencies in our screened control sample, in which a history, family history or current presentation of psychosis were exclusion criteria. Out of 348 control samples we detected a total of 4 CNVs in 4 samples (2 sided  $p=0.13$ ,  $OR=3.16$  (95% CI 0.90 to 11.04)). We stratified for deletions, where none were observed in the psychotic cases group and 2 CNVs in 2 samples were observed in the screened control group (2 sided  $p=0.51$   $OR=0$  (95%CI 0 - 4.75)), and duplications, where 5 CNVs in 5 cases were observed in the psychotic cases group

and 2 CNVs in 2 samples were observed in the screened control group (2 sided  $p=0.023$ ,  $OR=6.36$  (95% CI 1.40 -  $\infty$ )).

Several very large variants were observed in this dataset. See supplementary information for further details.

### Phenotypic Association Analyses

CNVs >100kb, called with at least 10 markers, in high quality samples and called using three algorithms were considered in this analysis, to minimise the effect of false positive calls clustering in different sample groups. Of 3,106 samples, 2,397 cases (77.2%) (717 male and 1,680 female) passed sample quality control. Phenotypic data was available in 1,940 (80.1%) of these samples. Eysenck personality trait questionnaire data was not available in the GENDEP study, which limited our analysis in these instances to a sample of 1,631.

1,337 rare CNVs were detected, of which 648 (48.5%) were deletion CNVs and 689 (51.5%) were duplication CNVs. 106 CNVs fell within regions previously associated with schizophrenia. Of these, 36 (34.0%) were deletion CNVs and 70 (66.0%) were duplication CNVs. 402 CNVs were defined as singleton events (i.e. occurring only once in the dataset). Of these, 205 (41.7%) CNVs were deletions and 287 (58.3%) duplications. Results for whole genome CNV association analyses with phenotypes are presented in table s4, analyses of singleton CNVs in table s5, and analyses restricted to CNVs within previously associated regions of the genome in table s6.

Age of onset data was available in 1,926 samples (98.7%). No significant association was found between global rare CNV burden per sample and age of onset of disorder. A non-significant trend was found between the number of rare CNVs falling over regions previously associated with schizophrenia and increased age of onset of disorder ( $t=2.12$ ,  $p>|t|=0.03$ ) (table 3). Re-analysing by region, this association was driven by duplications in 15q13.3 ( $t=1.9$ ,  $p>|t|=0.06$ ) (table s9). No significant association was found between singleton CNV burden and age of onset of disorder.

Duration of worst episode data was available in 977 samples (50.3%). No significant associations were found between measures of rare CNV burden and duration of worst episode.

Eysenck Personality Questionnaire data was available in 1,631 samples. Trait neuroticism data was available in 1,580 samples (96.9%), trait psychoticism data in 1,619 samples (99.3%) and trait extraversion scores in 1,619 samples (99.3%). No significant associations were found in any analyses between personality trait scores and CNV burden.

<<Table 3 about here>>

### **Whole Genome Burden Analysis**

This dataset is similar to the dataset used for our previous research(20) in which we showed evidence that samples with genic deletion CNVs over 100kb in size were more common in RDD cases than controls. We decided to re-visit this hypothesis using this dataset, which is subject to more stringent QC parameters and uses 3 algorithms to call CNVs, rather than 1. 2,397 cases, 332 screened controls and 2,151 WT2 controls passed sample QC. In comparison to our original results, we found no evidence to support the notion that CNVs are more common in RDD cases, but deletion CNVs in cases tended to harbor more genes in RDD cases than controls. A full table of results is shown in table s13. Briefly, whilst there were no significant differences between the proportion of samples to harbor a deletion CNV (2 sided  $p=0.55$ ), the deletion CNVs that were seen contained significantly more genes in cases than controls when control cohorts were combined (2 sided  $p=0.0002$ ), and independently, and in the same graduated manner observed in our previous analysis. A trend suggesting duplication events were more common in control samples was seen (2 sided  $p=0.049$ ), however the absolute difference was modest.

### **Discussion & Conclusions**

We present an analysis of large CNVs and chromosomal aneuploidies in a case-control sample of RDD. After correction for multiple testing, we generally find little

evidence for the association of large CNVs with RDD. We found an enrichment of undiagnosed Turner's syndrome in RDD cases when compared to a large population sample ( $n=34,910$ ) of live born infants taken in Denmark. We find further examples of other sex chromosome abnormalities and autosomal UPD in the case sample. We also present an analysis of global CNV burden. In a re-analysis of rare CNVs over 100kb, there was little evidence of differences in major measures of CNV burden, however the number of genes falling within deletion CNVs seen was significantly higher in cases than in both control groups, even after correction for multiple testing. When large CNVs >1MB in size were considered in isolation, we found they occurred more frequently in the case sample when compared to the screened control sample and to the WT2 control sample, but this difference fell short of statistical significance. The increase in frequency was driven by large duplication CNVs. A further association analysis with phenotypic measures found a non-significant trend between the burden of duplication events over regions previously associated with schizophrenia and increased age of onset. This was driven by duplications in the region 15q13.3. CNVs of this size are usually rare, and therefore we may lack power to detect an effect. An aggregated association analysis of CNVs is also hampered by pleiotropy in the regions studied; however without a greatly increased sample size, analysing by region is invariably underpowered. We present both methods of analysis here.

Some evidence already exists for the enrichment of sex chromosome aneuploidies in psychiatric disorders. One of the largest studies was published by Maclean et al. in 1968(38), where the buccal smear method(39) was used to distinguish between cells with chromatin bodies of various numbers in the different sexes. This technique does not reliably detect Turner's syndrome as it relies on the process of X inactivation to generate visible chromatin bodies. Nonetheless, this study found a significant enrichment of sex chromosome abnormalities amongst patients in psychiatric hospitals of the time when compared to a control population. However the inclusion of cases of schizophrenia, 'mental deficiency' and 'epileptic insanity' suggests a qualitatively different sample to our own. Mood disorders are known to be common in people with sex chromosome abnormalities(22), and therefore the

relative enrichment of cases of Turner's syndrome in our sample is unsurprising. The standardised mortality ratio for patients with Turner's syndrome who survive infancy is estimated to be 3.6(40) and thus the use of a live-born sample compared to a sample of adults is likely to underestimate the true difference. On the other hand, it is possible that the cases of mosaic 45,X/46,XX observed are derived from somatically acquired 45,X cells seen solely in blood. Overall, our results add evidence to the association of Turner's syndrome with RDD. There is little evidence for the association of Klinefelter's syndrome with mood disorders(22), and we found no evidence of this, although our sample probably lacks sufficient power (54.6% assuming a two-fold enrichment and a base population frequency of 1 in 1,000).

The detection of a diploid/triploid mosaic is notable. Previously rare, DNA microarray studies have already documented this phenomenon(41; 42). Individuals with congenital diploid/triploid mosaicism tend to be profoundly disabled(42; 43), and therefore are unlikely to have been included in our study. This variant is probably a somatically acquired abnormality.

Five instances of uniparental isodisomy (UPD), in chromosome 4 (2 cases); chromosome 12 (1 case); chromosome 13 (1 WT2 control); and chromosome 21 (1 WT2 control), were noted. UPD occurs when an individual receives two identical copies of a chromosome, or part of a chromosome, from one parent. Within the five instances of UPD observed in this sample set, all had LRR values indicating diploid copy number, whilst four out of five demonstrated complete loss of heterozygosity across the chromosome. This suggests the mechanism of monosomy rescue (by which chromosomal monosomy is avoided by duplication of the remaining chromosome during gametogenesis) and an origin in meiosis II(41). One sample demonstrated a resumption of heterozygosity at the distal end of chromosome 21q, suggesting partial recombination has taken place, and therefore an origin later in meiosis II(41). No significant differences in frequency were observed between the case and control samples, although we may be underpowered to detect an effect. The significance of these observations is not clear, although UPD is expected to disrupt imprinting and increase the chance of homozygosity for a recessive mutation(44).



In our previous analysis, we showed that rare deletion CNVs >100kb in length were significantly associated with our case sample, with a particularly low frequency of deletions being seen in our screened control sample(20). This study could be criticised for only using one calling algorithm for identification of CNVs between 100kb and 1MB. We reanalysed this dataset using more stringent QC parameters and 3 algorithms for CNV detection, as more recent research has shown that CNV algorithms are subject to high type 1 error rates(45-50). Our re-analysis indicates that whilst the proportion of samples containing CNVs is not significantly different between cases and controls, deletion CNVs within cases encompass significantly more genes than controls. It could be argued that restricting analysis to calls made by three algorithms is overly conservative, resulting in type 2 calling errors that reduce power to detect association. This dichotomy illustrates the tricky balance to be struck between known type 1 errors and unknown type 2 errors in CNV calling, which is likely to affect all analyses relying on indirect measures of genomic copy number.

In an attempt to clarify the relationship of CNV burden with RDD we analysed the relationship between CNV and phenotype using clinical measures taken during sample ascertainment. In general there were no statistically significant associations observed. A trend was observed between CNVs occurring over regions previously associated with schizophrenia and increased age of onset. This was driven by duplication events in the 15q13.3 region. The CNVs in this region all encompass the gene encoding the alpha 7 nicotinic cholinergic receptor (*CHRNA7*). This CNV has also been implicated in Alzheimer's disease(51) and a recent study (using some samples also included in this work) also found that this duplication was associated with a poorer response to antidepressant medication(52). Whilst the relevance of this observation to RDD is far from clear, its occurrence in association with age of onset in the context of other research implicating it in dementia and poorer response to antidepressants is notable, especially given the clinical crossover between depression and dementia observed in older adults(53). A full table of results and illustrations of the CNVs in these areas, can be found in the supplementary information.

The small sample size of screened control samples is a significant limitation to this study. This occurred because most subjects in this cohort contributed DNA via cheek swab, which we have found to be of insufficient quality to call CNVs reliably.

Furthermore, whilst our case sample is large, it is probably not of sufficient size to definitively determine the role of this level of genomic variation in this clinical group.

In summary, this study adds little evidence to the notion that rare CNVs are associated with RDD (in contrast to our previous analysis) although deletion CNVs that do occur in this group were shown to harbour more genes than deletion CNVs occurring in controls. This may be a relevant finding, since deletion CNVs, with concomitant loss of function, are expected to be more deleterious than duplications. Occasional large CNVs and chromosomal aneuploidies are seen in isolated cases. We found no evidence to suggest that duration of worst episode and personality traits as measured by the EPQ are associated with rare CNVs in cases of RDD, and other trends for significance fall short after correction for multiple testing. Generally speaking, the evidence for the involvement of CNVs in cases of mood disorders appears much less convincing than that for autism and schizophrenia. Genetic pleiotropy and sample heterogeneity in mood disorder samples, as well as the equivocal results from current studies, suggests that much larger sample sizes will be required to conclusively decide whether this level of genomic variation is of relevance. CNV meta-analyses from world-wide collaborations of large sample sets, particularly the psychiatric GWAS consortium(54), may shed further light on this issue.

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### **Conflicts of Interest**

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report; however, Michael Barnes was employed by GSK when the research was performed. James Rucker and Gerome Breen had full access to all data in the study and had final responsibility for the decision to submit for publication. Katherine Aitchison, Anne Farmer and Peter McGuffin have received consultancy fees and honoraria for participating in expert panels for pharmaceutical companies including GlaxoSmithKline. Anne Farmer has received travel and subsistence from GlaxoSmithKline to attend principal investigator planning, training and inter-rater reliability meetings. Katherine Aitchison also declares interests (all prior to September 2011) through Advisory Boards for Johnson & Johnson, Lundbeck, Roche Diagnostics, and Bristol-Myers Squibb; membership of Bristol-Myers Squibb UK Steering group 2003 to 2011;

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# Tables

	Cases		Pop. Controls		WT2 Controls		Screened Controls	
Clinical status/Sex	Female	Male	Female	Male	Female	Male	Female	Male
Normal	2,194	907	17,017	17,832	1,354	1,344	281	178
45,X	3		3*		0		0	
47,XXX	0		18		0		0	
47,XXY		2		20		1		0
Total	4		44		1		0	
Total by sex	2,197	909	17,038	17,872	1,354	1,345	281	178
Total	3,106		34,910		2,699		459	

Table 1. Frequency of sex chromosome aneuploidy in cases, 34,910 live-born infants from table 1 of Nielsen and Wohler(26)(Pop. Controls), WT2 controls and screened controls. \*This value was derived from the number of infants with 45,X syndrome (n=1) and 45,X/46,XX mosaic syndrome (n=2).

	Sample. No. of CNVs (No. of samples (%))		
	RDD Cases N=2,723	Screened Controls N=348	WT2 Controls N=2,359
All CNVs	77 (74 (2.71%))	4 (4 (1.10%))	45 (45 (1.91%))
Deletion CNVs	21 (20 (0.73%))	2 (2 (0.55%))	13 (13 (0.55%))
Duplication CNVs	56 (54 (1.98%))	2 (2 (0.55%))	32 (32 (1.36%))

Table 2. Frequencies of large (>1MB) CNVs and, in brackets, frequencies of samples with large CNVs in our datasets, stratified by type.

Phenotype	CNV Type	No. Samples	t	P> t
Age of Onset	All	1,926	2.12	0.03
	Deletions	1,926	1.35	0.18

	Duplications	1,926	1.64	0.10
Duration of Worst Episode	All	977	-0.56	0.58
	Deletions	977	-0.14	0.89
	Duplications	977	-0.57	0.57
Neuroticism	All	1,580	-1.74	0.08
	Deletions	1,580	-0.53	0.60
	Duplications	1,580	-1.71	0.09
Extraversion	All	1,619	1.68	0.09
	Deletions	1,619	1.72	0.09
	Duplications	1,619	0.92	0.36
Psychoticism	All	1,619	-0.21	0.83
	Deletions	1,619	0.57	0.57
	Duplications	1,619	-0.58	0.56

Table 3. Phenotype-genotype association results for tests between phenotype and CNVs falling over regions of the genome previously associated with schizophrenia. P values falling below 0.05 are highlighted in bold. P values falling below 0.0073 (corrected significance) are highlighted in bold italics.

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